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EXAMINER

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1642

DATE MAILED: 08/20/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

DETAILED ACTION

1. Claims 19, 32-33 have been amended.
2. Claims 6, 9-18, 20, 22-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions. Election was made **without** traverse in Paper No. 11.
3. Claims 3-5, 7-8, 19, 21, 32-34 are under examination.
4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.
5. The following Office Action contains some NEW GROUNDS of rejection.

Rejections Withdrawn

6. The rejection of claims 3-5, 7-8, 19, 21, 23-34 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.
7. The rejection of claims 3-5, 7-8, 19, 21, 32-34 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

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inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in view of the amendments to the claims.

8. The rejection of claims 3-5, 7-8, 19, 21, 32-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in view of amendments to the claims and the new ground of rejection under 112 first paragraph.

9. The rejection of claims 7-8, 19, 21, 23, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Nagase et al (DNA Res. 2:167-174, 1995) is withdrawn in view of the new grounds of rejection.

10. The rejection of claims 3-5, 7-8, 19, 21, and 32-34 under 35 U.S.C. 103(a) as being unpatentable over Nagase et al (DNA Res. 2:167-174, 1995) as applied to claims 7-8, 19, 21, 32-33 above, and further in view of Campbell (Monoclonal antibody technology, Elsevier Science Publishers, Chapter 1, pages 1-32) and Sambrook et al (Molecular Cloning, A Laboratory Manual, Chapters 3 and 12, 1989) is withdrawn in view of the new grounds of rejection.

The following are NEW GROUNDS of rejections

Claim Rejections - 35 USC § 112

11. Claims 3-5, 7-8, 19, 21, 32-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to pharmaceutical compositions and compositions for treating and preventing cancer with the polynucleotides claimed.

The specification teaches the identification of a tumor antigen peptide, referred to as SART-3 (SQ ID NO:2). The specification further contemplates the use of the DNA molecule encoding the tumor antigen for the immunotherapy of cancer diseases (page 15-18) where "in theory, any method of gene therapy may be used for immunotherapy of cancer based on DNA" (page 16) both *in-vivo* or *in-vitro*. The specification does not enable treatment or prevention of any cancer with the polynucleotides of the invention.

One cannot extrapolate the teachings of the specification to the scope of the claims because the specification provides no exemplification of or guidance on how to

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use the claimed pharmaceutical (i.e. DNA vaccine) for immunization purposes with any predictability and to treat or prevent any cancer in a subject. With regards to tumor immunotherapy, the goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, gene therapy against tumors is highly unpredictable as underscored by Crystal, R.G. (Science, Vol. 270, October 1995, pages 404-410) who teaches that in tumor vaccine studies intended to evoke a tumor-directed immune response, there is no convincing evidence (other than anecdotal case reports) that tumors actually regress, despite the promising observations in experimental animals. In other words, humans are not simply large mice (page 409, 1st column). More recently, Tait *et al.* (Clin.Canc.Res., Vol. 5, July 1999, pages 1708-1714) revealed just how unpredictable gene therapy was in the clinical setting. The authors' prior phase I trial of 12 patients with extensive ovarian cancer treated with a retroviral vector expressing the BRCA1 splice variant (LXSN-BRCA1sv) demonstrated vector stability, minimal immune response, gene transfer and expression, and some tumor reduction in the patients (page 1708, 2nd column, 2nd paragraph). In contrast, the Phase II trial initiated in patients with stage III and IV grade ovarian cancer, showed a high preponderance for vector instability (vector was degraded rapidly), a rapid immunological response invoking neutralizing antibodies to the retroviral vector, and no clinical response to the therapy. Although the difference in response to the therapy may be attributed to differences in immunocompetence between the phase I and II patients (page 1712, 2nd column), the end result seems to indicate that further experimentation is necessary prior to the successful application of

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DNA vaccines, especially with the regards to cancer therapy. There is no suggestion in the specification that the expression of these antigens from the polynucleotide has resulted in autoantibodies against the antigen thus it would be highly unpredictable that administration of the polynucleotide that encodes the antigen as a cancer vaccine, into patients would lead to an effective immune response against the tumor. Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable for of skill in the art to use the pharmaceutical compositions or vaccine formulations as contemplated in the disclosure. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

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The response filed 6/6/03 has been carefully considered but is deemed not to be persuasive. The response states that the article of Miyagi et al (Clinical Cancer Res. 7:3950-3962, 2001, attachment to #14) describes the results of peptides derived from SART-3 were administered to cancer patients (see page 10-11 of response). In response to this argument, the reference is not on subject because the claims are directed to a polynucleotide administered to the cancer patient and the art does not address this application.

Claim Rejections - 35 USC § 102

12. Claims 7-8, 19, 21, 23, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Nagase et al (DNA Res. 2:167-174, 1995) as evidenced by Kurshid et al (Analytical Biochemistry 208:138, 1993, abstract).

The claims recite a polynucleotide of SEQ ID NO:1 or a nucleotide of 12 to 2900 of SEQ ID NO:1 wherein the polynucleotide encodes a tumor antigen wherein the tumor antigen protein gives rise to peptide fragments and bind to HLA antigen and are recognized by cytotoxic T lymphocytes and compositions comprising such. For this rejection the intended use of a pharmaceutical composition and pharmaceutical composition for treatments or prevention of tumor is given no patentable weight.

Nagase et al teach a molecule that encodes the identical protein of SEQ ID NO:2. The molecule is identical to the coding region of SEQ ID NO:1 except for one nucleotide (see the attached sequence alignment on the back of this office action). As

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is readily known in the art sequencing errors do exist in polynucleotide sequences as evidenced from Kurshid et al the error rate in nucleotide sequences in ESTs is 2.45 percent. This rate is within the error of one or two nucleotide bases in 3798 bases that are in SEQ ID NO:1. Thus because of errors in the sequencing of polynucleotides it would be concluded that the molecule of Nagase et al is the same as the molecule of the instant applications polynucleotide. In addition, it would be inherent that the protein of Nagase et al would give peptides that would bind to HLA antigen and be recognized by cytotoxic T lymphocytes.

Claim Rejections - 35 USC § 103

13. Claims 3-5, 7-8, 19, 21, and 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagase et al (DNA Res. 2:167-174, 1995) as applied to claims 7-8, 19, 21, 32-33 above, and further in view of Campbell (Monoclonal antibody technology, Elsevier Science Publishers, Chapter 1, pages 1-32) and Sambrook et al (Molecular Cloning, A Laboratory Manual, Chapters 3 and 12, 1989).

Claims 7-8, 19, 21, 32-33 have been described supra. Claims 3-5, and 34 recite an expression plasmid with the polynucleotide and a transformant transformed with the expression plasmid and a method of producing the protein. For this rejection the intended use of a pharmaceutical composition and pharmaceutical composition for treatments or prevention of tumor is given no patentable weight.

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Nagase et al has been described supra. Nagase et al does not teach an expression plasmid or a transformant with the expression plasmid. This deficiency is made up for in the teachings of Campbell and Sambrook et al.

Campbell teach that it is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it for basic research (see page 29).

Sambrook et al teach expression plasmids and host cells for expression of proteins.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have placed the DNA of Nagase et al in an expression plasmid to produce the protein.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have placed the DNA of Nagase et al in an expression plasmid to produce the protein because Campbell teach it is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it for basic research (see page 29). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have placed the DNA of Nagase et al in an expression plasmid to produce the protein because Sambrook et al teach expression vectors and methods of expression of the DNA for structural and biochemical analysis (see page 16.2). Thus, It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have placed the DNA of Nagase et al in an expression

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plasmid to produce the protein because it is routinely done in basic research to further characterize the protein.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The response filed 6/6/03 has been carefully considered but is deemed not to be persuasive. The response states that at the time of the present invention SART-3 was not known in the art to be a tumor antigen protein and there would not be any motivation to use SART-3 for treatment of cancer. As stated in the rejection the intended use of the polynucleotides for treatment or prevention is given no patentable weight for this rejection. Thus, the prior art only need teach the polynucleotide and motivation to place the DNA in a vector for expression which it does as stated above.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be

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reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879



LARRY R. HELMS, PH.D
PRIMARY EXAMINER

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1241 TTGTATGACACTTCTCTCCACCCCTGCACAGACATGTGCCCGTCATTCTTTTAATTTTA 3300
1312 AAAGATGAAATGGCAGATGCTAGTAATTCACAGAAATGGCTCTTGTGGGGTGGGTCTGA 3371
1301 AAAGATGAAATGGCAGATGCTAGTAATTCACAGAAATGGCTCTTGTGGGGTGGGTCTGA 3360
1372 GGGAAATCAGCTATATAACATTTGCTGGAGTTTGTTCATAGGGCTGTGCAATTTTATA 3431
1361 GGGAAATCAGCTATATAACATTTGCTGGAGTTTGTTCATAGGGCTGTGCAATTTTATA 3420
1432 TTATGTTTGTAAATGACATGTCAGCGTCTTTTCATGTTTCCATAAGCAGAAATATT 3491
1421 TTATGTTTGTAAATGACATGTCAGCGTCTTTTCATGTTTCCATAAGCAGAAATATT 3480
1492 GCAACATTTGTTTGTATAGGAATTTATTTGCCACCTGCTGGACTGTTTCTTTGCC 3551
1481 GCAACATTTGTTTGTATAGGAATTTATTTGCCACCTGCTGGACTGTTTCTTTGCC 3540
1552 TAGTGACTAGTGACCTGTGTTCTCTAAACATGAGTTTCAGCCCTTTGGTTTGTAAATA 3611
1541 TAGTGACTAGTGACCTGTGTTCTCTAAACATGAGTTTCAGCCCTTTGGTTTGTAAATA 3600
1612 CCATGTCAAATGCAAACTTCAATTTCCCTCATTTAGCTTTATAAAGTACGTTCTCTTC 3671
1601 CATGTCAAATGCAAACTTCAATTTCCCTCATTTAGCTTTATAAAGTACGTTCTCTTC 3660